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The dentate gyrus and the hilar revised - Conor Houghton

It is suggested that, in addition to pattern separation, the dentate gyrus and hilar region in the hippocampus perform memory selection and that the selectivity of the gating of memory by this circuit is modulated by the norepinephrine - glutamate loop described in the target article.

In the target article the authors propose that arousal modulates attention through a norepinephrine - glutamate feedback loop in local microcircuits. Here, I would like to suggest a specific microcircuit where this mechanism may be in operation: the granule cell - mossy cell loop in the dentate gyrus and hilar region of hippocampus.

It is commonly proposed that the CA3 region of hippocampus forms an auto-associative memory store for short and medium term memories (Marr, 1971; Gardner-Medwin, 1976; Levy & Steward, 1979; Hopfield, 1982; McNaughton & Morris, 1987; Rolls, 1989; Treves & Rolls, 1992). In this pictures, memories, in the form of patterns of activity in the entorhinal cortex, feed forward along the perforant pathway to CA3, activating a sparse subset of the CA3 pyramidal cells. Plasticity in the synapses of the recurrent network in CA3 and in the perforant pathway synapses onto CA3 neurons stores the memory so that it can be recalled: if a part of the same pattern of activity occurs in entorhinal cortex, the corresponding part-pattern is activated in CA3 by the perforant pathway and it is then completed by auto-associative dynamics.

Pattern collision, where two similar memories are confused during pattern completion, is a problem in auto-associate networks, particularly if they are required to rapidly store memories with only a small number of presentations. It is likely that the hippocampus has a mechanism to avoid or reduce pattern collision: the hippocampus stores rapidly acquired memories and it is important that similar but distinct memories can be distinguished during recall.

It has been proposed that the role of the dentate gyrus is to reduce the problem of pattern collision (Treves & Rolls, 1992; O'Reilly & McClelland, 1994; Gilbert, Kesner, & Lee, 2001; Leutgeb, Leutgeb, Moser, & Moser, 2007; McHugh et al., 2007). In addition to CA3 neurons, the perforant pathway connects to the granule layer in dentate gyrus. The granule layer of dentate gyrus is, in turn, connected to CA3 along the mossy fibres, that is, the axons of the granule cell. This means that the entorhinal cortex is connected to CA3 directly, along the perforant pathway, and indirectly, along the perforant pathway to the dentate gyrus and then along the mossy fibres to CA3. In the specific version of dentate gyrus pattern separation proposed in (O'Reilly & McClelland, 1994) there is local k-winner-take all dynamics between cells in dentate gyrus and the consequence of this is that only a random subset of the cells receiving input from entorhinal cortex become active. This activity is feed forward along the mossy fibers to CA3 and in turn, excites a random subset of those cells in CA3 that receiving input from entorhinal cortex. This randomisation separates the patterns that are then learned in the CA3 auto-associative network.

There is experimental evidence (McHugh et al., 2007) that the dentate gyrus is important for pattern separation and that the adult neurogenesis of dentate gyrus granule cells, which may support the randomisation, is linked to pattern separation (Altman, 1963; Bayer, Yackel, & Puri, 1982; Clelland et al., 2009; Sahay et al., 2011). However, it seems unlikely that pattern separation is the only role of the dentate gyrus; for a start, pattern separation on its own seems a modest role for such a substantial brain region. Beyond this, pattern separation does not explain either the hilar region or the role of norepinephrine in the dentate gyrus.

The hilar region lies between dentate gyrus and CA3. As the mossy fibers run through the hilar region they form *en passant* connection with the mossy cells (Amaral, 1978; Scharfman & Myers, 2012). These are large excitatory cells whose proximal dendrites are covered in mossy-looking spines. The mossy cells, in turn, have a substantial back-projection which extends along the longitudinal axis of the dentate gyrus (Amaral & Witter, 1989; Amaral, Scharfman, & Lavenex, 2007) and connects to both granule cells and inhibitory interneurons (Scharfman, 1994, 1995).

This two layer structure seems more elaborate than a simple randomising k-winner-takes-all network would require; random sub-selection from a pattern could be achieved by local excitatory-inhibitory dynamics within the dentate gyrus itself. However, the two-layer structure would make sense if the role of the dentate gyrus encompassed memory selection as well as pattern separation. As pointed out in (Koch & Ullman, 1984, 1987; Olshausen, Anderson, & Van Essen, 1993) a single layer winner-takes-all network in which competition occurs across the whole network requires considerable inter-neuronal connectivity. This is solved by having more than one layer; in the first layer competition is restricted to subregions, a champion emerges from each subregion to compete in the next layer where the competition between subregions occurs. In short, it is suggested here that, in addition to separating patterns, the winner-take-all dynamics in the dentate gyrus also compares the salience of different aspects of its input and that this selection gates and refines the storage of memories in CA3. The role of the hilar region is to facilitate this comparison.

The locus coeruleus projects to the dentate gyrus which contains beta-adrenegic receptors (Berridge & Waterhouse, 2003; Harley, 2007). Norepinephrine release in response to novelty during exploration enhances excitability in the dentate gyrus (Kitchigina, Vankov, Harley, & Sara, 1997), in fact, the activity of both interneurons (Nitz & McNaughton, 2004) and excitatory neurons (Neuman & Harley, 1983; Dahl & Winson, 1985) in dentate gyrus show norepinephrine-promoted increase in response to novelty. Furthermore, it has been shown that in hippocampus glutamate causes enhanced norepinephrine release (Pittaluga & Raiteri, 1990; Raiteri, Garrone, & Pittaluga, 1992), an effect which is most marked in the dentate gyrus (Andrés, Bustos, & Gysling, 1993). Conversely, norepinephrine in dentate gyrus, but not in other hippocampal regions, potentiates the release of glutamate (Lynch & Bliss, 1986).

The role of norepinephrine in dentate gyrus seems somewhat mysterious if the role of the dentate gyrus is restricted to pattern separation. However, if, as proposed here, the dentate gyrus also performs memory selection then the norepinephrine - glutamate mechanism for modulating memory selectivity described in the target article becomes the missing clue that could explain the role of norepinephrine in dentate gyrus.

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